Current perspectives on Guillain-Barré syndrome

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Background: **This article aims to review recent advances in the etiology, typing, pathogenesis and treatment of Guillain-Barré syndrome (GBS).**

Data sources: **Articles were searched in PubMed with the searching items related with Guillain-Barré syndrome.**

Results and Conclusion: **The commonly identified preceding pathogens have been identified such as *Campylobacter jejuni*, cytomegalovirus and others. Immunomodulating treatment has been proven to alleviate nerve damage and shorten the progression of the disease. GBS remains a serious disorder with a relatively high disability rate and a mortality, which definitely requires more effective treatment.**

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Key words: **Guillain-Barré syndrome; infection; neuropathy; Immunomodulating treatment**

Guillain-Barré syndrome (GBS) now ranks as the most frequent cause of acute flaccid paralysis since the near-elimination of poliomyelitis throughout the world and its median annual incidence is 1.3 cases per 100 000 population. GBS is an acute inflammatory polyradiculoneuropathy and commonly characterized by rapidly progressive, essentially symmetric weakness, areflexia, and the time of its inception to full progression is no longer than 4 weeks.[1]

This article briefly reviews some advances in the etiology, typing, pathogenesis and treatment of GBS.

Etiology

At present, the accurate etiology of GBS is not yet completely understood and a number of investigations indicate that it is an autoimmune inflammatory peripheral neuropathy which can be triggered by many factors including bacterial or viral infections, vaccinations, etc on the basis of host susceptibility.

Antecedent infections

Nearly two-thirds of GBS cases have a history of infection within 4-6 weeks before GBS onset, and respiratory and gastrointestinal infections are the two commonest antecedent infections. The commonly identified preceding pathogens are as follows.

Campylobacter jejuni (C. jejuni)

C. jejuni is a Gram-negative spiral-shaped bacterium that can cause diseases in humans and animals. Surveys have shown that *C. jejuni* as one of the leading causes of bacterial diarrhea throughout the world has also been recognized as the most frequent antecedent pathogen for GBS, especially in Japan and China; serological or culture evidences of *C. jejuni* infection can be found in around 67% of GBS patients.[2,3] Studies from other countries and regions showed that *C. jejuni* infection was detected serologically in 32% (the Netherlands), 23% (North America and Europe), 26% (South East England), and 38% (Australia) of GBS patients.[2,4-6] With a highly specific enzyme-linked immunosorbent assay, one research group from Germany found serological evidence of preceding *C. jejuni* infection in 80.6% of GBS patients but in only 3.5% of the controls, and they concluded that the role of *C. jejuni* in triggering GBS might have been greatly underestimated in the past.[7]

Penner's serotyping system divides *Campylobacter* species into over 100 types. HS: 19 strains are significantly over-represented in GBS patients, but this serotype is infrequent in patients with enteritis who do not develop GBS. Accumulative findings strongly indicate that certain *C. jejuni* strains trigger the development of GBS.[3]

C. jejuni infection frequently precedes GBS, but it is far more common than GBS. One general practice research database study demonstrated that the probability that an individual who develops *Campylobacter* enteritis will also develop GBS during the subsequent 2-month period is <2/10 000.[8] A few investigations provided clues that certain HLA types may be responsible for this. However, the definite association of GBS with *C. jejuni* infection and HLA is still controversial.[1,9,10]

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Cytomegalovirus (CMV)

CMV is the most common viral trigger of GBS, with a prevalence ranging from 10% to 22% in several studies in GBS patients. CMV-related GBS is characterized by a prominent involvement of the cranial and sensory nerves. A few reports indicated that patients with CMV-associated GBS have serum antibodies against ganglioside GM2.[11] Another study from Japan showed that anti-GM2 IgM antibodies were found in 22% patients with GBS after CMV infection.[12] More data are needed to verify the specificity of this antibody and its significance in the pathogenesis of CMV inducing GBS.

Other infectious agents

There have been many reports of GBS preceding infection pathogens including Epstein-Barr virus (EBV), *Mycoplasma pneumonia, H. influenza*, varicella-zoster virus, influenza virus, adenovirus, parainfluenza 1 virus, herpes simplex virus, HIV, etc. A multivariate analysis showed that in GBS patients, infections with EBV (10%) and *Mycoplasma pneumonia* (5%) were more frequent than in controls. In the same study, however, only approximately 1% GBS cases were found to be infected respectively with *H. influenza*, parainfluenza 1 virus, influenza A virus, influenza B virus, adenovirus, herpes simplex virus, and varicella-zoster virus.[6,13] Another report from Japan showed serological evidence of *H. influenza* infection in 13% of 41 consecutive patients with GBS. In recent years, it was occasionally reported that West Nile virus, Coxsackieviruses or *H. pylori* infections may also be associated with the development of GBS.[14-16]

Vaccinations

A limited number of case reports have suggested a possible link between GBS and vaccinations, such as influenza vaccination, hepatitis A vaccination, hepatitis B vaccination, rabies vaccine, oral poliovirus vaccine, tetanus-diphtheria-toxoid vaccine, measles-mumps-rubella vaccine, and meningococcal conjugate vaccine. However, accumulative data do not support the causal association between vaccinations and GBS. If any association exists, it must be rare and not of public health significance. So far, the evidence that immunizations trigger GBS seems to be weak, and the benefits of vaccination outweigh the risks of vaccine-inducing GBS.[1]

Other antecedent events

Some other rare GBS associated antecedent events have been reported such as surgery, cancer, pregnancy, autoimmune diseases, use of drugs, spinal anesthesia, non-Hodgkin's lymphoma, insect stings, leigh syndrome, epidural-general anesthesia, surgery for obesity, olanzapine administration and transplantation operations. Several cases have been found to develop GBS after therapeutic injection of bovine brain ganglioside preparations.[17]

Host immunogenetic background

In comparison with the above relatively common antecedent events, the risk of developing GBS following them actually is very low. Experiencing the same preceding events, why only very few cases present GBS-like neuropathy? Some findings indicated host susceptibility may be a determinant for the occurrence of GBS. Many studies have attempted to identify the association between the occurrence of GBS and a particular HLA type. In the past three decades, about twenty studies investigating HLA distribution in GBS patients have been reported including the following HLA alleles: HLA-DR3, HLA-DQB1*03, HLA-B54 and Cw1, HLA-DQB1*0401, HLA-DRB1*04, and HLA-DRB1*01.[9,10] More recently, however, a large-scaled case-control study failed to find an association between HLA-DR and HLA-DQ molecules and disease susceptibility. The authors concluded that the HLA system probably did not play a general role in the susceptibility to develop GBS, but they still interestingly found an probable association between HLA-DRB1*01 and mechanical ventilation of GBS.[1,10] Another team reported that susceptibility to develop GBS may be associated with polymorphisms of CD1E and CD1A genes.[18] In summary, no definitive conclusion has yet been reached about immunogenetic factors responsible for the development of GBS and further research is needed to investigate these factors involving in the disease process.

Subtypes of GBS

GBS's peripheral nerve damage can be histopathologically classified into two main types: demyelination and axonal degeneration. Motor nerve fibers are more susceptible to the disease than sensory ones. In 1995, GBS was subdivided into four main distinct forms based on histopathological and neurophysiological properties.[19,20]

Acute inflammatory demyelinating polyradiculoneuropathy (AIDP)

AIDP accounting for 80%-90% of GBS cases in Europe and North America is characterized by an immune-mediated attack on myelin with various degrees of lymphocytes and macrophages infiltration, and segmental stripping of myelin. Motor and sensory fibers are usually affected simultaneously and produce corresponding neurological deficits. Electrophysiological studies show slowed nerve conduction velocities and prolonged F wave.

Acute motor axonal neuropathy (AMAN)

AMAN, entirely a motor form of neuropathy, is most prevalent in China and Japan (50%-60% of cases), but it is encountered in western countries with a much lower frequency (10%-20% of cases). AMAN is characterized by axonal degeneration in which axons appear to be the main target of the immune attack and commonly occurs within 1-2 weeks after antecedent infections.

Specific binding of antibodies to the axonal membrane of motor fibres, predominantly at the nodes of Ranvier, complement activation, and intrusion of macrophages into the periaxonal space result in destruction of motor axons while lymphocytic infiltration is rare. Gangliosides have been considered as the most promising candidate targets. *C. jejuni* is the commonest preceding infectious agent, and the increasing level of anti-ganglioside antibodies is usually found in this type of GBS.[19]

The main electrophysiological features are reduction of muscle action potentials, relatively preserved motor nerve conduction velocities, and normal sensory nerve action potentials and F wave.

Acute motor and sensory axonal neuropathy (AMSAN)

AMSAN is an axonal disorder similar to AMAN with the exception that the sensory nerves are also involved. This subtype is very few (less than 10% of AMAN cases) and its pathological pattern closely resembles that in AMAN, including damage and degeneration of axons, except that sensory nerves are affected simultaneously. AMSAN is usually associated with a more severe course and poorer prognosis.[19,21]

Miller Fisher syndrome (MFS)

MFS is an infrequent variant of GBS (around 5%). The involvement of the cranial nerves is very distinct in this syndrome, and ocular motor (oculomotor, trochlear, and abducens) nerves are usually affected and produce typical clinical triad of ophthalmoplegia, ataxia, and areflexia. Histopathological studies are generally rare due to lack of nerve biopsy data. Nerve conduction velocities are often normal. Another important feature of MFS is a close to 100% incidence of characteristic serum autoantibodies against gangliosides GQ1b and GT1a. Therefore it seems that antibodies against GQ1b most likely play a key role in the pathogenesis of MFS.[21]

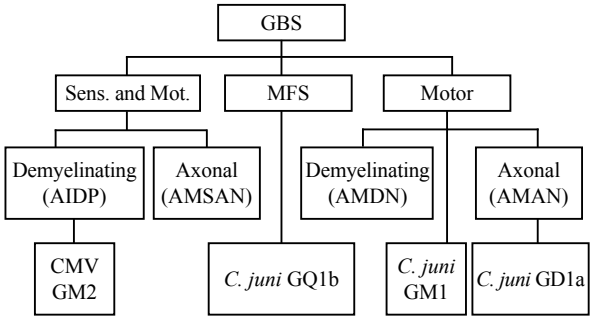

Fig. Steps in classifying clinically defined GBS (From Van der Meché et al. Eur Neurol 2001)

Van der Meché et al[22] considered acute motor demyelinating neuropathy (AMDN) as another type of GBS, and proposed a 4-step-method in classifying clinically defined GBS (Fig.).

Besides the above main forms of GBS, acute pandysautonomia is also a relatively common subtype characterized by the rapid onset of combined sympathetic and parasympathetic failure without sensory and motor involvement. Moreover, there is a number of other well-characterized but uncommon regional variants including pure ataxic GBS, pharyngeal-cervical-brachial GBS, and isolated bulbar palsy.[19]

There are two other inflammatory demyelinating polyneuropathies that need to be discriminated clinically from GBS, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and subacute inflammatory demyelinating polyradiculoneuropathy (SIDP). These three disorders are distinguished mainly according to the period of disease progression.

CIDP is a symmetrical sensory-motor neuropathy with demyelinating features on EMG and an increased cerebrospinal fluid protein, which progress clinically for at least 8 weeks, a main difference from GBS. CIDP also has several subgroups, and intravenous immunoglobulin (IVIG) and PE are effective for this disorder too. Unlike GBS, however, it is generally accepted that steroids are effective in CIDP.

SIDP was first reported in 1978 to describe a group of GBS-like patients with a progressive phase of demyelinating neuropathy lasting between 4 and 8 weeks but cannot be classified into either GBS or CIDP. Recently, some researchers reported the clinical, electrophysiological and histological characteristics of SIDP and presented the diagnostic criteria of this disorder: the diagnosis of "definite SIDP" was made when all four of the following mandatory criteria were met: progressive motor and/or sensory dysfunction consistent with neuropathy in more than one limb with time to nadir between 4 and 8 weeks; electrophysiological evidence of demyelination in at least two nerves; no known etiology of neuropathy other than associated diseases; and no relapse on adequate follow-up. Adequate follow-up required at least 2 years. Supportive criteria included S1, high spinal fluid protein level of >55 mg/dl and S2, specific nerve biopsy finding of inflammatory neuropathy. The diagnosis of "probable SIDP" may be made when demyelinating neuropathy has progressed over a period

of 4 to 8 weeks.[23]

The term of SIDP bridges the gap between GBS and CIDP. SIDP has all the characteristics of CIDP with three exceptions: a higher rate of antecedent infection, no relapse rate, and a high rate of recovery to normal. SIDP is more sensitive to corticosteroids monotherapy comparing with GBS.[23,24]

Pathogenesis

No precise pathogenesis of GBS is well elucidated up to now, but GBS is considered an organ-specific immune-mediated disorder emerging from a synergistic interaction of cell-mediated and humoral immune responses to still incompletely characterized peripheral nerve antigens. Each subtype of GBS presumably has a relatively independent immunopathogenesis.

Acute inflammatory demyelinating polyradiculoneuropathy

Demyelination is the most typically pathological feature of AIDP and its immune target is mainly within the myelin. There are prominent lymphocytic infiltration in the peripheral nerves and macrophage invasion in the myelin sheath and Schwann cells. Cellular immunity is of critical importance in the pathogenesis of this form of GBS.[1,19,25]

It has long been known that this commonest form of GBS characterized by segmental demyelination of the peripheral nerves, which is caused by macrophage-mediated stripping of the myelin sheath. Since it was first reported in 1955 by Waksman and Adams, experimental allergic neuritis (EAN) has been widely used as an animal model to investigate the mechanisms of AIDP and has yielded many important experimental insights into the pathogenesis of this disorder.[26-30] The key roles of T cells and macrophages have been demonstrated by several studies including adoptive transfer EAN (AT-EAN). The findings emphasize the important contributions of cellular immunity to the development of AIDP.[19,31-36]

Increasing studies in GBS patients and EAN may partly reveal the complex process of inflammatory lesions in the peripheral nerves:[19,25,37] autoreactive T-cells recognize a specific autoantigen presented by major histocompatibility complex class II molecules and the simultaneous delivery of costimulatory signals on the cell surface of antigen-presenting cells, such as macrophages, in the systemic immune compartment. Activated T-lymphocytes can cross the blood-nerve barrier in order to enter the peripheral nervous system. Within the peripheral nervous system, T-cells activate macrophages that enhance phagocytic activity, production of cytokines, and the release of toxic mediators, such as nitric oxide, matrix metalloproteinases, and proinflammatory cytokines, propagating demyelination and secondary mild axonal loss.[19,38-43]

In contrast to the axonal subtype of GBS, however, the putative antigenic target molecules within the myelin in AIDP remain elusive and further research is needed. Some pathogens have been reported to precede this disorder including CMV and EBV.

Acute motor axonal neuropathy

AMAN is pathologically characterized by axonal Wallerian degeneration, suggesting an immune response directed primarily against the axonal membrane. Reversible conduction block at the nodes of Ranvier may also play a role in the pathogenesis of AMAN. *C. jejuni* is the commonest antecedent infection of AMAN, which is frequently associated with anti-ganglioside antibodies (GM1, GM1b, GD1a or GalNAc-GD1a).[1,19,44] Various observations suggest that humoral factors are of paramount importance in the development of AMAN.

"Molecular mimicry" is very important to understand the pathogenesis of this form of GBS. In 1993, Yuki et al[45] first reported the existence of molecular mimicry between nerve tissue and *C. jejuni* that elicits GBS. Their study showed that the terminal structure of *C. jejuni* lipooligosaccharide (LOS) is identical to that of the terminal tetrasaccharide of GM1 ganglioside. Since then, numerous reports confirmed their results and increasing studies demonstrated some other oligosaccharide structures of GM1b-like, GD1a-like, and GalNAc-GD1a-like LOSs in *C. jejuni* strains isolated from GBS patients. Recently, another term "carbohydrate mimicry" is also proposed to describe this structure similarity. Rabbit immunization studies indicate a key role for this molecular mimicry in the pathogenesis of *C. jejuni* associated GBS, and sialic acid may be crucial for the *C. jejuni* LOS induced anti-ganglioside antibodies.[5,46-53] It was demonstrated that some other preceding pathogens including CMV, EBV, *Mycoplasma pneumoniae* also have carbohydrate sequences (antigens) in common with peripheral nerve tissues.[54]

This humoral immune response is that autoantibodies, crossing the blood-nerve barrier or locally produced by B-cells, attack directly the nodal axolemma or activate the complement system resulting in axonal damage and slight demyelination. Macrophages penetrate the basal lamina of Schwann cells and enter the periaxonal space, eventually resulting in the axons degeneration. Lymphocytic infiltration is absent. Some researchers reported that neuromuscular junction may be another important site for antibody action.[1,19,55]

Acute motor and sensory axonal neuropathy

AMSAN, another axonal subtype of GBS, has similar features with AMAN except that the patients have prominent sensory involvement besides motor nerves axonal degeneration. Only a few anti-ganglioside antibodies including anti-GM1, anti-GM1b, and anti-GD1a IgG antibodies have been found in a limited number of patients.[56,57]

Miller Fisher syndrome

MFS is usually regarded as a variant of GBS, and increased serum titers of antibodies to GQ1b and GT1a are consistently found in 90% and 100% of patients respectively. GQ1b is enriched in human ocular-muscle nerves, which may account for the vulnerability of these nerves to humoral immune mediated attack in the MFS patients apart from the involvement of some other factors in its pathogenesis.[19]

Treatment

It is important to estimate the severity of GBS patients for treatment considerations. The Hughes functional grading scale is widely used to evaluate clinical disability and the functional endpoint[58] (Table.). Treatment of GBS can be subdivided into supportive care, immunomodulating, pain management and rehabilitation.[1,59]

Supportive treatment

Approximately 25%-30% of patients with severe GBS have to be monitored or subjected to mechanical ventilation.[1] The patients should be monitored in the ICU if they are dysautonomic, Hughes disability scale score ≥ 3 or <3 progressing. Intubation should be carried out if the patients developing bulbar dysfunction and aspiration. A detailed flowchart has been proposed for the use of clinical and respiratory factors in the management of GBS.[60]

Immunomodulating treatment

Effective immunomodulating treatment can lessen nerve damage, reduce progression, and shorten hospitalization.

Table. Hughes functional grading scale for GBS (From Hughes et al, Lancet 1978)[58]

Score	Description
0	Healthy
1	Minor symptoms or signs, able to run
2	Able to walk 5 m independently
3	Able to walk 5 m with a walker or support
4	Bed- or chair-bound
5	Requiring assisted ventilation
6	Death

Plasmapheresis and IVIG are the mainstay of immunomodulatory treatment at present. Both treatments have proven to exhibit beneficial effects in various controlled trials by favorably altering the natural course of the disease. Their effectiveness is similar and both appear to be more effective than supportive treatment alone. Corticosteroids are still a doubtful topic in the treatment of GBS.

High-dose immunoglobulin

The empirical dose of IVIG generally used for the treatment of GBS is 0.4 g/kg per day for 5 days. There was a non-significant trend toward a better outcome noted in the group receiving longer treatment of 6 days, and this trend reached significance when only ventilated patients were considered, but the shorter course such as 3 days was proven to be significantly less effective.[61-63] In pediatric patients with GBS, IVIG significantly hastens the recovery of patients and has also been found to be effective and safe. Thus, its efficacy, safety, and availability make IVIG the treatment of choice in many patients with GBS.[64,65]

The mechanisms of action of IVIG have not been fully understood, but it is known that IVIG has multiple functions including downregulation of antibody production, acceleration of antibody metabolism, neutralization of complement-mediated effects, interference with antibody-dependent cytotoxicity mediated by macrophages, modulation of nitric oxide production and microglial function, direct effects on T-cell activation, inhibition of cell adhesion, and induction of apoptosis. Any or all of these could be the predominant mechanisms of IVIG in the treatment of GBS.[1,19,66]

Plasma exchange (PE)

PE is the first immunomodifying therapy proven to be effective in the treatment of GBS. Two exchanges are better than none for mild GBS, for moderate GBS as well as for severe cases. Four plasma exchange sessions are sufficient, further sessions are not helpful if there is no response to IVIG or if there is further deterioration during this treatment. The PE regimen involved exchange of approximately one plasma volume, 50 ml/kg. There are more adverse events with fresh frozen plasma as the replacement fluid than albumin. Five percent albumin solution is commonly used as the replacement solution unless there is an increased risk of bleeding, then fresh frozen plasma will be more appropriate.[1,63,67-70]

PE has an acceptable safety profile when the patient's condition is carefully monitored but is nonetheless not entirely free of risk, especially in hemodynamically unstable patients and in those with infectious complication. Such risks as well as the high cost and the limited number of plasma exchange facilities result in less

common PE than IVIG in pediatric clinics.

Variations of plasma exchange have been developed to improve its safety; immunoadsorption and double filtration plasmapheresis are chosen to avoid risks of infection and allergic reaction. CSF filtration has also been performed. However, none of these studies showed any significant difference in outcome compared to PE.[62]

Combined treatment of PE and IVIG is not significantly better than either alone. Therefore, sequential treatment with PE followed by IVIG is not recommended.[1,69]

Corticosteroids

Corticosteroids are widely used to treat many autoimmune disorders and once expected to be effective for GBS. However, the majority of trials showed no benefit from corticosteroids.[69] A Dutch trial suggested the combination of intravenous methylprednisolone followed by IVIG hastens the recovery of GBS patients slightly more than IVIG alone. There is another report showing that corticosteroids may be effective against pain from GBS. Because of lack of more findings that support the efficacy of corticosteroids in GBS, corticosteroids are not recommended or at least should not be used alone in the treatment of GBS.[1,69,71]

Other treatments

Pain was reported in 89% of GBS patients; 75% of them additionally required oral or parenteral opioids and 30% were treated with intravenous infusion of morphine.[72] Ten percent of the patients received tricyclic antidepressants and a further 10% received carbamazepine as adjuvant treatment for neuropathic pain during the later phase of the illness. Carbamazepine and gabapentin may also be effective in the management of pain, and epidural infusion of morphine may be helpful in controlling intractable and severe pain.[72]

Rehabilitation is necessary for the recovery of GBS patients. Treatment in the acute phase should include an individual program of gentle exercises involving isometric, isotonic, isokinetic, and manual resistive and progressive resistive exercises. Rehabilitation should be focused on proper limb positioning, posture, orthotics, and nutrition.[72]

Remission occurs in 70% of the patients though half of them remain mildly affected, being better in younger patients.[73] Ten to twenty percent of the patients have a disability and mortality rate of 5% and 10% respectively.[4,17,72-75] A few GBS patients could finally turn out to have CIDP.[75-77]

Conclusions

GBS is now histopathologically subdivided into four types: AIDP, AMAN, AMSAN and MFS. SIDP has been defined by some investigators to describe a group of GBS-like patients whose progressive course lasting between 4 and 8 weeks but cannot be classified into either GBS or CIDP.

Accumulating evidence strengthens the molecular mimicry theory in the pathogenesis of AMAN and increasing preceding pathogens have been identified in the past 10 years, *C. jejuni* is the commonest reported antecedent infection and sialic acid may be crucial for the *C. jejuni* LOS inducing neuropathy. All of these findings further the understanding of pathophysiology of this clinical syndrome though more research is needed to reveal its precise mechanism. Though the immune target of AIDP has been identified mainly within the myelin for a long time, the putative antigenic molecules remain elusive. A few antecedent infectious agents except CMV have been determined. Searching for the pathogens, the antibodies and antigenic molecules in AIDP are required to validate this theory in its development.

Immunomodulating treatment has been proven to alleviate nerve damage and shorten the progression of the disease. IVIG and PE seem to be similar effective for GBS patients. Despite these treatments, GBS remains a serious disorder with a relatively high disability rate and mortality, which definitely requires more effective treatment.

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